IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Sadelain et al.	
Application No.: 08/940,544	
Filed: 9/30/1997	Group Art Unit: 1642
Title: Fusion Proteins of a Single Chain Antibody and CD28, and Uses Thereof	Examiner: Larry Ronald Helms
Attorney Docket No.: MSK.P-035	

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the rejection mailed 6/18/2003. The claims of this application have been more than twice rejected. Accordingly, an appeal of a non-final rejection was appropriate. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is Sloan-Kettering Institute for Cancer Research.

Related Appeals and Interferences

To Applicants' knowledge, there are no related appeals or interferences.

Status of Claims

Claims 1-20 have been presented in this application. Claims 1, 2, 6 and 7 stand rejected. Claims 3-5 are objected to as dependent on a rejected base claim, but are otherwise considered allowable. Claims 8-20 are withdrawn from consideration.

Status of Amendments

All amendments in this case have been entered.

Summary of Invention

The claims of this application are related to a fusion protein. As set forth in claim 1, the encoded fusion protein comprises

(a) a single chain antibody comprising the variable region of a light chain of a selected antibody and the variable region of the heavy chain of the selected antibody;

(b) the signaling domain of human CD28 receptor; and

(c) a transmembrane domain, wherein the transmembrane domain is disposed between the single-chain antibody and the signaling domain. In the specific embodiment of claim, the transmembrane domain is the transmembrane domain of human CD28. Claims 6 and 7 recite an additional element of the polynucleotide, namely a suicide gene such as thymidine kinase, that allows selective and controlled termination of cells expressing the fusion protein.

The recombinant polynucleotides of the invention are useful in the induction of an immune response to the selected antibody. It has been proposed that transformation of T cells *ex vivo*, and their reintroduction into a patient could form a way for developing an immune response to tumor cells that are normally not recognized by the immune system. As noted in the specification, one of the difficulties encountered when such systems have actually been tested, however, is the ability of the transformed cells to undergo clonal expansion, that is to be copied so that the immune response persists, following reintroduction. The recombinant polynucleotides of the present invention are useful for making genetically-modified T cells with enhanced survival and enhanced cytotoxic activity *in vivo*. These T cells can be used to induce an immune response to cells, particularly tumor cells, when express the antigen for which the antibody is specific.

Issues on Appeal

1. Are claims 1 and 2 anticipated under 35 USC § 102(b) by Eshhar et al., WO93/19163?

2. Are claims 1 and 2 anticipated under 365 USC § 102(e) by Roberts et al, US 5,686,281?

3. Would claims 1, 2, 6 and 7 have been obvious over the teaching of Eshhar in combination with the teachings of Sambrook?

4. Would claims 1, 2, 6 and 7 have been obvious over the teaching of Roberts in combination with the teachings of Sambrook?

Applicants submit that all of these questions should be answered in the negative.

Grouping of Claims

With respect to the first issue, claims 1 and 2 are argued as a group and stand or fall together.

With respect to the second issue, claims 1 and 2 are argued as a group and stand or fall together.

With respect to the third issue, claims 1, 2, 6 and 7 as a group and stand or fall together.

With respect to the fourth issue, claims 1, 2, 6 and 7 as a group and stand or fall together.

Argument

Claims 1 and 2 are not anticipated by Eshhar

Applicants submit that Eshhar is not an anticipatory reference with respect to the claimed invention as defined in claims 1 and 2. The reasons for this is three fold. First, Eshhar

does not teach a specific embodiment within the scope of the claims. Second, Eshhar does enable the making of a species of a recombinant polynucleotide within the scope of claims 1 or 2. Third, Eshhar does not provide a "written description" of a recombinant polynucleotide within the scope of claims 1 and 2.

The Teaching of Eshhar

Eshhar describes "chimeric receptor gene: that can be used to "endow[] lymphocytes with antibody type specificity." (Page 1, lines 7-9). These genes encode a fusion protein formed from a single chain antibody, a flexible linker, and a gene segment "encoding a short extracellular and the entire transmembrane and cytoplasmic domain of a lymphocyte-activation molecule." (Page 7, lines 10-14). A lengthy list of lymphocyte-signalling domains is provides that includes TCR signalling components, and also other lymphocyte-signalling chains, which are listed as zeta and eta chains of CD3, the gamma chain of the FcγR and FcεR, the α,β, and γ chains of the IL-2R or any other lymphokine receotpr, CD16 α chain, D2, and CD28." (Page 8, lines 31-36).

The actual examples of found in Eshhar are not as broad as the laundry list of possible receptor types. For example, Eshhar provides a specific disclosure of an scFV-CD16α fusion. CD16 is a receptor that binds to complexed IgG to stimulate NK killer activity. Eshhar also talks about fusions containing TCR signalling components. These components are involved in generating an activation signal as a result of interactions with adjacent chains expressed by the same T-cell.

Eshhar fails to actually teach a CD28 containing fusion or the nucleotide encoding it.

In order for an anticipation rejection to be proper, the reference "must unequivocally disclose the claimed compound or direct those skilled in the art to the claimed compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 172 USPQ 524, 526 (CCPA 1972). In this case, the claimed compound of claims 1 and 2 is a recombinant

polynucleotide with three recited parts. One of these parts is the CD28 signalling domain. Another is a transmembrane domain, that can be a CD28 transmembrane domain. CD28 is mentioned only twice in the Eshhar reference, once on Page 8, and again on Page 18. The description of Fig. 1 (page 9) does not state that the R portion of that molecule can be CD28 (or CD2, the other mentioned costimulatory molecule). In short, there is no specific description, or picture of any molecule that includes a portion of CD28. This disclosure is insufficient to teach a compound within the scope of the present invention, without inference or guesswork. Thus, Eshhar is not properly considered to be anticipatory.

Eshhar Does Not Provide an Enabling Disclosure

In order to be anticipatory, the reference relied upon must provide an enabling disclosure. *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990). As previously noted, Eshhar contains minimal examples, none of which relate to CD28 containing fusions. These examples are not enabling of CD28, and therefore cannot be relied upon as anticipatory of the present claims. In response, the Examiner asserts that the mere mention of CD28, combined with a disclosure of a scFV-CD16α fusion is enough to provide an enabling disclosure. No indication of similarities between CD28 and CD16 are given by the Examiner, nor any reasoning beyond the bare assertion. This is not sufficient to establish a sound basis for the stated assertion of the Examiner.

CD16 is a receptor that binds to complexed IgG to stimulate NK killer activity. In contrast, CD28 is a co-stimulatory factor in T cell activation that interacts with B7 on B cells and certain antigen presenting cells. Eshhar provides an example (Fig. 19) of a construct in which a portion of the **α-subunit** of CD16 is used with an scFv to make a fusion protein. CD28 does not have multiple heteromeric subunits so it is not apparent how this teaching would be applied in the context of CD28. Indeed, the Examiner has not offered any reasons why CD16 and CD28 would be deemed so similar by a person skilled in the art that the characteristics of a fusion incorporating CD16 would offer any expectations about likelihood of success, or a teaching of how to accomplish a functional fusion with the other. Eshhar also teaches specific examples of

fusion proteins in which a T-cell receptor chain is part of the fusion. These molecules also function differently than CD28, since they interact with other parts of the TCR to provide activation, not a co-stimulatory signal.

It is also ironic that the scope of enablement which the Examiner states is provided by the reference far exceeds the scope of enablement which the Examiner originally acknowledged for this application. In the Office Action dated 1/27/00, the Examiner offered various reasons for lack of enablement of the pending claims, including that the construct needs to be in the proper orientation for signaling function of CD28, and that there are no working examples in the allegedly unpredictable art. (Page 10). Eshhar's disclosure with respect to CD28 is nothing more than a single entry in a listing of multiple possible receptor's and can in no way be deemed to meet the standards for enablement which the Examiner asserted were appropriate. There is no reference to a known sequence of CD28, no example of primers for extracting appropriate portions of CD28, and no teaching with respect to workable orientations of CD28. Furthermore, Eshhar itself sets the CD28 (and CD2) apart on the basis of function from the types of receptors that are specifically shown. As such, there is no basis to conclude that Eshhar provides an enabling disclosure for CD28 containing fusions.

An Anticipatory Reference Must Provide a "Written Description" of the Claimed Invention

This case raises an issue that appears to be one of first impression with respect to the requirements for an anticipatory reference. It is well established that in order to anticipate a claim, the reference relied upon must disclose each and every element of the claimed invention It is also well established that in order to be relied upon as anticipatory, the reference must provide an enabling disclosure of at least one embodiment of the invention as claimed. Further, anticipation cannot be found where selections from among alternatives are required, in order to arrive at the claimed invention.

What has not been addressed before is whether a disclosure that fails to provide a "written description" of an embodiment of the invention, as that phrase in 35 USC § 112, second paragraph has recently been discussed by the Court of Appeals for the Federal Circuit, is

sufficient to be considered an anticipatory reference.[1] The issue of whether a reference must provide a "written description" of an invention in order to be anticipatory represents an important understanding within the field of patent law, particularly as it pertains to biotechnology. Already, perhaps in an attempt to respond to the new embellishments of written description, applications are appearing in which a known sequence is transcribed to expressly list every conceivable combination of say 15 bases (i.e., 1-15, 2-16, 3-17 ...). The inventors in such cases have made at most a few of these molecules, and know nothing about the properties of the others. Yet, since there would be no difficulty making a mere 15 bases nucleotide sequence with current technology, such a disclosure does not fail to serve as an anticipatory reference under the enablement requirement. Only by requiring that the reference also provide a written description of the invention can the patent law avoid depriving actual inventors of selected embodiments within such lists from the fruits of their labors, and avoid providing a disincentive for research and development. Stated differently, the test for anticipation has always been whether the reference placed the public in possession of an Applicants' invention. How can a reference accomplish this if it does not even show that the author of the publication had "possession" of the invention. Thus, a "written description" of the invention should be a requirement for any reference that is to be asserted as anticipating a claimed invention.

Eshhar Does Not Provide a Written Description of CD28

Containing Fusion Proteins or the Nucleotides Encoding Them

In *University of Califormia v. Eli Lilly Co.*, the Federal Circuit observed that "a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The Court also stated that:

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[1] *See, University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997); *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002); *Moba B.V. v. Diamond Automation Inc.*, 66 USPQ2d 1429 (Fed. Cir. 2003).

> an adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention". Fiers v. Revel , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

43 USPQ2d at 1404. Eshhar does not meet this standard of written description.

As noted above, Eshhar mentions CD28 only twice in the application, and provides no examples of fusion proteins containing CD28. There are no diagrams of such a fusion protein or nucleotide (CD28 not being included in the list related to Fig. 1), and no sequences of a protein or polynucleotide that includes CD28. Thus, there is no written description of the present Applicants' invention in Eshhar, and Eshhar should not be considered as anticipatory art.

The Patent Office and the courts have advanced the policy that disclosure of partial nucleotide sequences and a method of how to proceed from there, even if enabling, is not sufficient to provide written description support for certain types of biotechnology inventions. The Eshar reference does not even provide this level of teaching with respect to the CD28 fusions. Instead, it says only that other fusions besides the exemplified γ and ζ-containing fusions can be made, and includes CD28 as one of a list of possible choices.

Application of this concept in this case clearly comports with fundamental fairness. The actual examples in Eshar relate to fusions containing two types of T-cell receptor (TCR) chains. These receptors are involved in generating an activation signal based on interaction with adjacent chains that physiologically associate with the TCR. In contrast, CD28 must interact with a ligand (B7) displayed on B cells and other professional antigen presenting cells or dendritic cells and macrophages, and produces a multiplicity of effects. Without actually making such fusions and performing experiments, one could not know whether or not the expressed CD28 (assuming a given fusion provided expression) would associate with

supramolecular complexes as does the native protein, nor could it be known whether of not the CD28 fusion would provide all of the functionality of native CD28.

Roberts Does Not Provide an Anticipatory Disclosure

For much the same legal reasons as Eshhar, Roberts (US 5,686,281) fails to provide a disclosure that anticipates claims 1 and 2 of the present invention. The Roberts patent discloses fusions of an extracellular binding domain, a transmembrane domain and a signaling domain which may be derived from CD28. The patent asserts that essentially anything with binding function can serve as the extracellular binding domain, and mentions scFv as a possibility. However, the patent provides no specific examples of scFv-containing fusions nor any specific teaching of how to make such fusions specifically. It also provides no evidence that such fusions function as asserted, nor any relationship besides binding function between scFv and the extracellular domains that are actually shown to work. Thus, this patent does not provide either an enabling disclosure or a written description of applicants' invention, but merely a generalized statement submitted to justify a generic claim. Such a disclosure would not be deemed to a claim as specific as that now pending, and therefore it should not be sufficient to serve as an anticipatory reference.

The Obviousness Rejections

The Examiner also rejected claims 1, 2 6 and 7 as obvious over the combination of either Eshhar or Roberts in view of Sambrook. The Sambrook reference is cited for a general teaching of the use of suicide genes, and the Examiner argues that adding such a gene into a polynucleotide of Eshhar or Roberts would have been obvious. This rejection, however, improperly relies on the appropriateness of the anticipation rejection. The Examiner has not addressed what the primary references suggest about a CD28 containing fusion, or the extent to which the properties of such a fusion would be predictable from the art. Thus, no *prmia facie* case of obviousness has been presented.

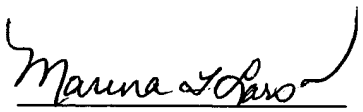
While it is possible that a non-enabling reference may be used as part of an obviousness rejection, even where insufficient for an anticipation rejection (*See, e.g., Symbol*

Technologoies, Inc. v. Opticon, Inc., 19 USPQ2d 1241 (Fed. Cir. 1991), the secondary reference here does not overcome the difficulties of the Eshhar and Roberts references with regard to enablement and written description. At best, the primary references provide an invitation to experiment, with no clear cut expectation of the nature of the product, or whether it will be effective for any purpose. Furthermore, in the context of obviousness, it should be noted that neither Eshhar nor Roberts provides any actual information about the characteristics of their products when confronted with apoptotic stress. Thus, there is no basis to predict the properties of Applicants' claimed fusions, and in particular the fact that the signaling function is shown to be effective to maintain living cells in the presence of inducers of apoptosis.

Conclusion

For the foregoing reasons, Applicants submit that the rejections of claims 1, 2 6 and 7 should be reversed.

Respectfully submitted,



Marina T. Larson Ph.D.
PTO Reg. No. 32,038
Attorney for Applicant
(970) 468-6600

CLAIMS ON APPEAL

1. A recombinant polynucleotide encoding a fusion protein, wherein the fusion protein comprises

(a) a single chain antibody comprising the variable region of a light chain of a selected antibody and the variable region of the heavy chain of the selected antibody;

(b) the signaling domain of human CD28 receptor; and

(c) a transmembrane domain, wherein the transmembrane domain is disposed between the single-chain antibody and the signaling domain.

2. The recombinant polynucleotide of claim 1, wherein the transmembrane domain is the human CD28 transmembrane domain.

3. The recombinant polynucleotide of claim 1, wherein the selected antibody is an anti-G_{D2} antibody.

4. The recombinant polynucleotide of claim 3, further comprising a suicide gene.

5. The recombinant polynucleotide of claim 4, wherein the suicide gene encodes thymidine kinase.

6. The recombinant polynucleotide of claim 1, further comprising a suicide gene.

7. The recombinant polynucleotide of claim 6, wherein the suicide gene encodes thymidine kinase.

Withdrawn Claims

8. A recombinant peptide comprising the variable region of the light chain of a selected antibody linked to the variable region of the selected antibody, the signaling domain of the human CD28 receptor and a transmembrane domain.

9. The recombinant peptide of claim 8, wherein the transmembrane domain to the human CD28 transmembrane domain.

10. The peptide according to claim 9, wherein the selected antibody is an anti-G_{D2} antibody.

11. T cells expressing a recombinant peptide comprising the variable region of the light chain of selected antibody linked to the variable region of the heavy chain of the selected antibody and to the signaling domain of the human CD28 receptor and a transmembrane domain.

12. T cells of claim 11, wherein the transmembrane domain to the human CD28 transmembrane domain.

13. T cells according to claim 11, wherein the selected antibody is an anti-G_{D2} antibody.

14. T cells according to claim 13, wherein the T cells further express a suicide gene.

15. T cells according to claim 14, wherein the suicide gene encodes thymidine kinase.

16. A method for inducing in a host an immune response to tumor cells expressing a surface antigen comprising the steps of

(a) transducing T cells to introduce an expressible recombinant polynucleotide encoding a fusion protein comprising the variable region of the light chain of an antibody against the surface antigen, linked to variable region of the heavy chain of an antibody against the surface antigen, the signaling domain of human CD28 receptor and a transmembrane domain; and

(b) introducing transduced T cells expressing the recombinant polynucleotide into the host.

17. The method according to claim 16, wherein the transmembrane domain to the human CD28 transmembrane domain.

18. The method of claim 16, wherein the tumor cells express G_{D2} as a surface antigen, and wherein the fusion protein includes the light chain and the heavy chain of an antibody against G_{D2}.

19. The method according to claim 18, wherein the expressible polynucleotide further encodes a suicide gene.

20. The method according to claim 19, wherein the expressible polynucleotide further encodes a suicide gene.